Inappropriate Vasopressin Secretion (SIADH) in Burned Patients

KHAN Z. SHIRANI, M.D., GEORGE M. VAUGHAN, M.D., GARY L. ROBERTSON, M.D.*,
BASIL A. PRUITT, JR., M.D., WILLIAM F. McMANUS, M.D., ROOSEVELT J. STALLINGS, M.D., AND
ARTHUR D. MASON, JR., M.D.

To determine if concentration of plasma arginine vasopressin (AVP) is inappropriate for the plasma Na⁺ concentration in hyponatremic burned patients, we obtained 32 plasma samples from 20 patients with total burn size (TBS) 15 to 80% of body surface on or after postburn day (PBD) 4 in the morning following all-night recumbency. In the 25 samples (17 patients) with hyponatremia, AVP was elevated, 1.6 to 14.3 (normal < 0.5) pg/ml. Most patients with normal serum Na⁺ had normal AVP values. Out of the total, nine patients (12 samples) without renal failure or sepsis, selected also for hyponatremia and urinary Na⁺ ≥ 20 mEq/L, were considered separately. BUN of 11.7 ± 1.8 mg/dl and plasma glucose of 130 ± 5.6 mg/dl, Na⁺ of 130 ± 1.1 mEq/L, calculated osmolality of 272 ± 1.6 mosm/kg, and cortisol of 20.4 ± 1.6 μg/dl were associated with a 24-hour fluid intake of 4.3 ± 0.26 L and urinary output of 2.7 ± 0.33 L, Na⁺ of 80 ± 14 mEq/L, and osmolality of 520 ± 73 mosm/kg (mean ± SE). In all of the plasma samples, AVP was markedly elevated (6.9 ± 1.1 pg/ml). In another study, four hyponatremic burned patients were given a standard water load. Excretion of the water was delayed, and further dilution of the initially hypotonic plasma resulted in a fall of urinary osmolality and plasma AVP. Cutaneous thermal injury can cause resetting of the mechanism linking plasma tonicity and AVP secretion resulting in dilutional hyponatremia. This syndrome occurs in the absence of gross physiologic perturbations such as volume depletion or adrenal insufficiency.

Antidiuresis in the first 24 to 36 hours following trauma has been observed for many years and was reviewed by Dudley et al. (7). Using major surgery as a model, these authors also found marked water retention in the first 1 to 2 days after surgery that could be mimicked by administration of exogenous posterior pituitary extract. They proposed that post-traumatic antidiuresis was not entirely explained by sodium retention but resulted from secretion of antidiuretic hormone (ADH) and suggested that confirmation of this mechanism awaited an assay for ADH.

Soroff et al. (26) found that exaggerated antidiuresis often exists for days and weeks after burn injury. They observed that in burned patients exhibiting a fall in serum Na⁺ concentration, there was an associated administration of greater amounts of electrolyte-free water than in other burned patients. Adequate urine flow (mean 2.7 L/day), appreciable Na⁺ excretion (64 mEq/L) and positive Na⁺ balance indicated that a deficit of fluid volume or of Na⁺, a possible cause for water retention, was not a factor in these cases. Instead, they suggested that hyponatremia in the presence of burn injury is dilutional and speculated that it results from an osmoregulatory mechanism set at a lower than normal plasma tonicity.

Following this, the clinical syndrome of inappropriate secretion of antidiuretic hormone (SIADH) was described in patients with cancer, disorders of the central nervous system, and diseases of the lung, and the clinical criteria for the diagnosis of SIADH were defined (4). Collentine et al. (5) reported three burned patients exhibiting the criteria of hyponatremia and hypotonic plasma, urine not maximally dilute, and normal renal and adrenal function. They suggested that burn injury could cause SIADH.

Subsequent development of a radioimmunoassay for plasma ADH (arginine vasopressin, AVP) allowed confirmation of elevated plasma AVP as the mechanism of classical SIADH (21). Application of AVP assays to plasma of burn victims (9, 15) has been limited to the first postburn week and has demonstrated very high concentrations of AVP in the presence of high plasma tonicity. Initially high plasma osmolality may have resulted from the fluid shifts that occur just after injury and during the first few days when fluid resuscitation is the prime goal of therapy. However, by postburn day 4 to 6, one can see in these data a suggestion of low plasma tonicity at a time when plasma AVP was still elevated. In those studies, serum Na^+ concentrations were not presented, and in one (9), it was stated that serum Na^+ stayed within normal limits. Thus the possibility of SIADH was not evaluated in those studies.

We have focused our attention on burned patients with hyponatremia occurring after the third postburn day when circulating volume has been restored (18). Measurements of plasma AVP corroborate the presence of SIADH in these patients.

Fig. 1. Plasma Na^+ and AVP concentrations in burned patients. The lines connecting two symbols indicate the same patient sampled on two different mornings. The stippled area represents the normal range (G.L. Robertson, unpublished). UNa^+, urinary Na^+ concentration. Creat., creatinine concentration. L.D., least detectable AVP level.

MATERIALS AND METHODS

Patients. Men aged 17 to 63 years were studied on postburn day (PBD) 4 to 58, with initial total burn size (TBS) of 15 to 80% of the body surface area. Before their accidental burn injury, they had no history of previous endocrine or renal disease. They were resuscitated according to a modified Brooke formula (19) in the first 48 hours after injury. Subsequently, fluids and electrolytes were administered to replace losses in a manner guided partly by urine flow and determinations of body weight, electrolytes, urea nitrogen, and creatinine in serum and urine. A large caloric intake (estimated resting metabolic rate, +25%) was begun in the first week. Morphine was given, if required for pain. Wounds were treated with alternate application of mafenide acetate in the morning and silver sulfadiazine in the evening. When eschar excision and grafting occurred before our studies, at least 5 days elapsed before the patient was studied. Samples were taken after overnight recumbency and before breakfast or other elements of routine care were given.

Analyses. Electrolytes, urea nitrogen, glucose, and creatinine levels were determined in serum and urine by standard procedures. Plasma cortisol was determined by radioimmunoassay. Osmolality was determined by freezing point depression. Plasma arginine vasopressin (AVP; antidiuretic hormone) was determined by radioimmunoassay (20).

Study I (Figs. 1-3). Blood was sampled from 20 burned patients for determination of electrolytes and AVP in plasma. Patients were included if they were in the intensive care area or if they were known to have been hyponatremic. Some patients were sampled on two separate mornings for a total of 32 samples. Urine sam-
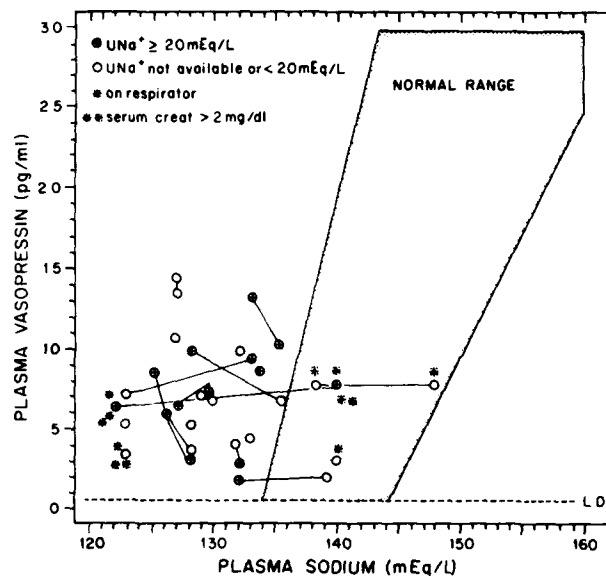
ples were also obtained on some of these occasions for determination of Na^+ and osmolality. The relationship between plasma Na^+ and AVP was compared to that in a large group of uninjured normal subjects (Fig. 1). In order to eliminate volume deficit and other factors as explanations for possibly elevated AVP values, 12 samples from nine patients (TBS 15 to 48%, PBD 4 to 21) with hyponatremia, serum creatinine $\leq$ 1.3 mg/dl, urinary Na^+ $\geq$ 20 mEq/L, normal blood pressure and chest radiographs, and absence of clinical evidence of sepsis (ileus or obtundation) were considered separately (Figs. 2 & 3). Cortisol was determined in the plasma samples. Because plasma osmolality was not measured in these patients, it was calculated from the concentrations of the significant osmotically active plasma components ($2Na^+$ + BUN/2.8 + glucose/18). In addition, fluid intake and urinary output were determined for the 24 hours immediately preceding the time of plasma sampling for the study.

Study II (Figs. 4-6 and Table I). Four other patients (TBS 21 to 42%, PBD 9 to 37) with hyponatremia and normal BUN and serum creatinine levels were given a water load orally, 20 ml/kg body weight, over 20 minutes. Na^+ concentration and osmolality were measured in plasma and in hour-long urine collections taken before and for 4 to 6 hours after the beginning of water ingestion. AVP concentration was also determined in plasma. Patient 1 had *H. influenzae* epiglottitis and pneumonia at the time of study and was on a respirator with inspiratory assistance and a positive end-expiratory pressure of 3 cm of water. The other three patients had no pulmonary disease or sepsis at the time of study. Patient
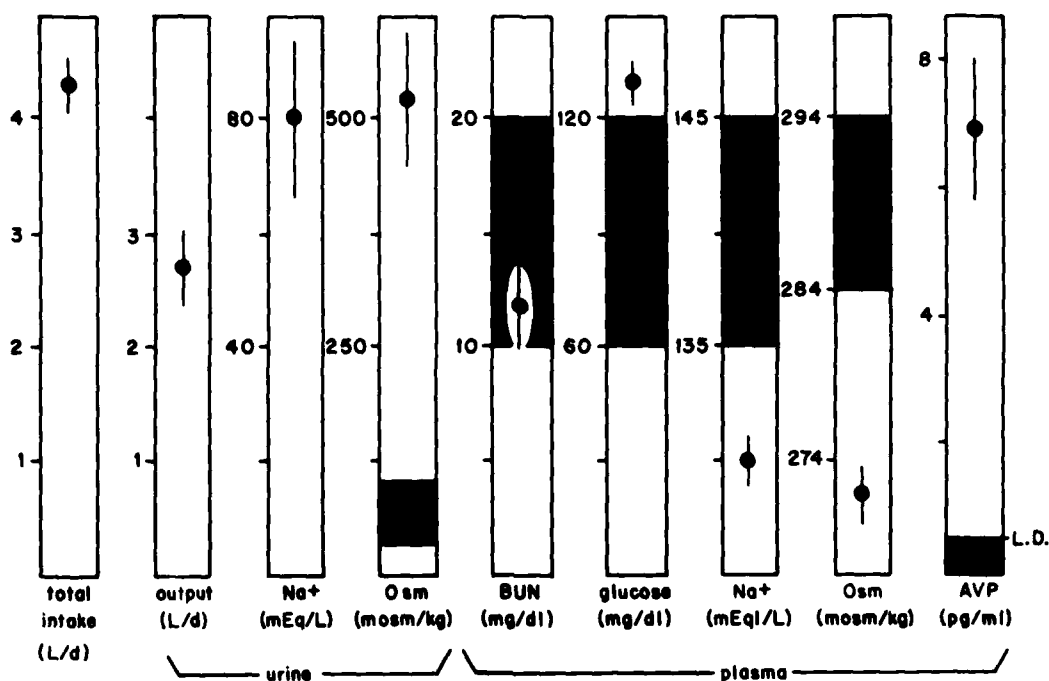
Fig. 2. Urinary and plasma (mean ± SE) values in 9 patients with normal renal function, hyponatremia, and urinary Na$^+$ concentration ≥ 20 mEq/L. Blocked areas indicate the normal ranges. For urinary osmolality (Osm) and plasma AVP, the normal ranges for hypotonic plasma are given.
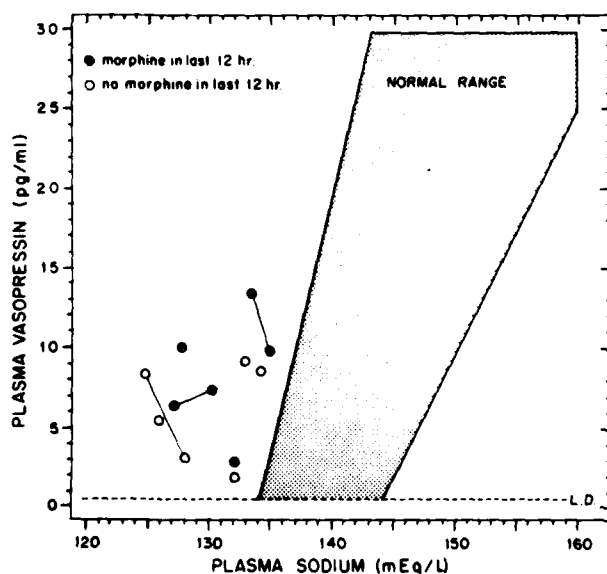

Fig. 3. Comparison of plasma Na$^+$ and AVP concentrations for the individual patients of Fig. 2. The normal range and lines connecting symbols are explained in the Fig. 1 legend.

Fig. 4. Oral water loading tests performed in four hyponatremic burn patients. The baseline sample is indicated by the patient number, and subsequent samples are 1 hour apart. The last two samples of patient 4 were obtained during infusion of 5% NaCl. The range for normal subjects was taken from the literature (16).

4 had a Swan-Ganz catheter placed the day before for determination of pulmonary wedge pressure and cardiac output by thermodilution. In this patient, 4 hours after ingestion of the water load, an infusion of 5% NaCl, 0.05 ml/kg per minute, was given for 2 hours, and plasma Na$^+$ and osmolality were determined at 20-minute intervals.

RESULTS

Study I. In 27 plasma samples, AVP was elevated beyond that anticipated for the plasma Na$^+$ concentration in uninjured normal subjects (Fig. 1). In 25 samples (17 patients), hyponatremia (Na$^+$ 123 to 134 mEq/L) was present and AVP ranged from 1.6 to 14.3 (normal < 0.5) pg/ml. Only two of these patients, both of whom were on respirators and one of whom was hypotensive and receiving a dopamine infusion, had elevated serum creatinine levels. Of seven samples (six patients) with plasma Na$^+$ 135 to 148 mEq/L, five samples (four pa-

FIG. 5. Cumulative urinary volume excreted during the water loading tests. Patient numbers are indicated at the right. The range for a large group of normal subjects is shown (22).

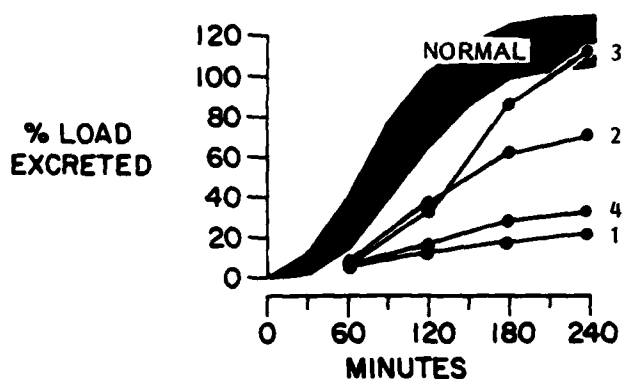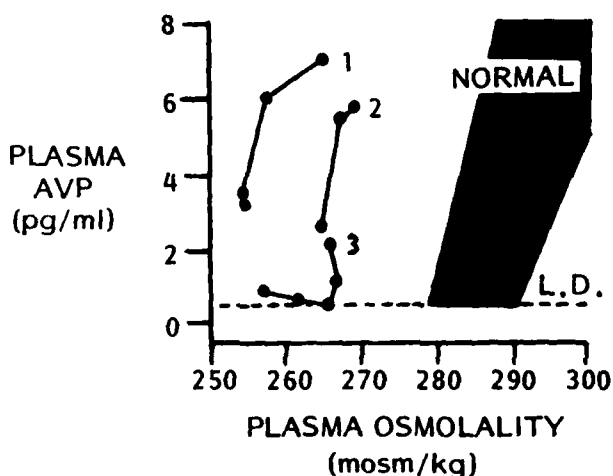FIG. 6. Comparison of plasma osmolality and AVP during the water loading tests in Patients 1–3, for time points at which AVP values were obtained (see Table I). The points are connected on the basis of proximity to one another, not necessarily representing the time sequence. AVP values for Patient 4 are not available. L.D., least detectable AVP level. The normal range is indicated (22).

TABLE I

Patient No.	Age (yrs)	Sex	TBS (%)	PBD	Time (hr)	Posm (mosm/kg)	AVP (pg/ml)
1	58	M	20.5	11	−1	267	
					0	265	7.0
					1	254	
					2	255	3.2
					3	255	
					4	254	3.6
					5	256	
					6	257	6.1
2	25	M	17.0	9	−1	269	
					0	269	5.9
					1	261	
					2	267	5.5
					3	268	
					4	265	2.6
3	63	M	29.0	37	−1	269	1.5
					0	267	1.1
					1	257	0.8
					2	262	0.7
					3	266	0.5
					4	266	2.1

AVP values for the water loading tests in Patients 1–3. The water load was given orally just after the time 0 sample. TBS: total burn size. PBD: postburn day. Posm: plasma osmolality.

patients exhibited diluted plasma and concentrated urine (Fig. 4), hyponatremia (plasma Na$^+$ range, 127 to 133 mEq/L), and detectable urinary Na$^+$ (96, 19, 105, and 10 mEq/L, respectively, for Patients 1 through 4). Patient 4, who had a Swan-Ganz catheter and in whom a 2-hour infusion of 5% NaCl followed the water loading test, had a pulmonary wedge pressure of 13 mm Hg at baseline and 17 mm Hg 6 hours later at the end of the NaCl infusion. Cardiac output, obtained only at baseline, was 17.2 L/minute in this patient. Figure 4 shows that after the water load, further reduction in measured plasma osmolality was followed by a reduction in urinary osmolality in every case. However, relative concentration of urine with respect to the plasma, together with delayed excretion of the water load (Fig. 5), indicates the propensity for water retention in these patients. Patient 3, who responded with the greatest urinary dilution (although at an abnormally low plasma tonicity) also finally excreted the water load by 4 hours. At the beginning of the test, systolic blood pressure (mean ± SE for the 4 patients) was 147 ± 3, diastolic was 74 ± 2 mm Hg, and heart rate was 120 ± 7/min.

For Patients 1 through 3, plasma AVP values were obtained during the test (Fig. 6 and Table I). The data from these patients confirm the observation from Study I that plasma AVP concentration is inappropriately elevated for the plasma tonicity in hyponatremic burned patients. Reduction of plasma osmolality was accompanied by a fall in AVP concentration. For Patient 2, the major decrement in plasma osmolality at 1 hour was not reflected again at 2 hours and, since AVP was not sampled at 1 hour, an initial fall in AVP may have been

tients) had AVP values in the normal range for the plasma Na$^+$. Three of these patients with normal AVP were on respirators, one of these had an elevated serum creatinine, and another was hypotensive and receiving dopamine.

In the group of nine uncomplicated patients (Figs. 2 & 3) selected for hyponatremia and urinary Na$^+$ ≥ 20 mEq/L, concentrations of plasma cortisol (range, 13 to 32 μg/dl) were in the normal range (7 to 25 μg/dl) or elevated. Despite appreciable urine production and Na$^+$ excretion, the low plasma Na$^+$ concentration and calculated plasma osmolality were associated with a high measured urine osmolality (Fig. 2). Figure 3 shows that in each sample, plasma AVP was elevated (> 0.05 pg/ml) for the Na$^+$ concentration, whether or not morphine was given for pain in the preceding 12 hours. Morphine had not been given within 24 hours before collection of four of the samples (in three patients).

Study II. Just before the water loading test, these

missed. However, the smaller decrement in plasma osmolality at 4 hours (possibly due to delayed absorption of the water load or variable absorption from edematous burn wounds) was associated with a lower AVP concentration.

DISCUSSION

Observation of hyponatremia and hypotonic plasma in burned patients in the presence of hypertonic urine confirms the case reports of Collentine et al. (5) and indicates that classical SIADH can occur in burned patients. Furthermore, elevated AVP concentrations have been observed in these patients and can be lowered by further dilution of plasma, with a fall in urine concentration. These results indicate that in patients with burn injury, the SIADH is the result of measurably elevated plasma concentrations of AVP and that the threshold for AVP secretion is set at a lower than normal plasma tonicity. Normal or elevated plasma cortisol concentrations indicate absence of adrenocortical failure, a potential cause for water retention and SIADH (11).

Plasma concentrations of norepinephrine and epinephrine are markedly elevated in burned patients (30). However, it is unclear what net effect this might have on AVP secretion, because infusion of norepinephrine inhibits, whereas infusion of isoproterenol stimulates, water retention in dogs, apparently through alterations in AVP secretion (24). Hypothyroidism is associated with elevated plasma AVP (25). Although burned patients typically have low plasma concentrations of total and free triiodothyronine, the metabolic significance of this is not known, because burned patients are hypermetabolic (30).

Angiotensin II, particularly in vitro with posterior pituitary tissue or when given by the intracerebroventricular route, can promote the secretion of AVP in animals (24, 28, 29). Plasma renin activity (despite normal plasma volume and Na^+ excretion) (23) and angiotensin II concentrations in plasma (6) are reportedly elevated in burned patients. Thus, there is some likelihood that elevated plasma angiotensin II, possibly resulting from elevated sympathetic activity or from as yet unidentified stimuli, may be a factor in SIADH of burn injury.

Although morphine or opioids have been shown to inhibit (8, 13, 17, 28, 29) or promote (10, 14) AVP secretion, morphine administration did not appear to be a necessary factor in the elevated plasma AVP concentrations in these burned patients. Pain is also an unlikely factor, because those not requiring morphine denied being in pain.

Because blood flow to the burn wound is increased (2), one might consider whether this shunt results in a decreased flow to noninjured areas and consequently a decrease in effective arterial volume which could stimulate AVP release. However, the available evidence suggests that areas outside the injury do not have compro-

mised flow. Muscle blood flow 7% higher (not statistically significant) in burned patients compared to controls has been reported (3). In burned patients in a study of peripheral blood flow, blood flow in an uninjured leg was 14% higher (not statistically significant) than in control subjects (2). The kidney may be of particular interest, because an experimental arteriovenous shunt may produce a reduction in renal plasma flow and creatinine clearance (27). But, blood flow in the splanchnic bed of burned patients was markedly elevated to twice normal values, and renal blood flow in burned patients was normal with Na^+ excretion < 40 mEq/day and elevated with greater Na^+ excretion (1). Glomerular filtration rate is reportedly elevated in burned patients (12). Because of increased gluconeogenesis, burned patients have elevated urea production (31). Thus the BUN values in the lower normal range and appreciable urine volumes in our patients further suggest adequate effective volume. Whether the hypermetabolic state and increased O_2 demand (31) influence the adequacy of the effective arterial flow with respect to AVP control mechanisms is not known, and this may represent one of the difficulties in assessing the role of effective arterial flow in the SIADH of burn injury. Tachycardia, a feature of the hemodynamic status after burn injury, by itself has a diuretic effect, apparently through reduction of AVP secretion (24). Since this is a response opposite to the antidiuresis seen in burned patients, tachycardia does not explain the SIADH in these patients.

Thus the SIADH in burned patients seems not to be a result of gross physiologic perturbations such as adrenal failure or volume contraction. Several potential mechanisms may be fruitful areas for future investigation, including the net effect of elevated plasma catecholamines and angiotensin II and reduced thyroid hormone concentrations. In addition, the possibility of reduced effective arterial volume relative to increased metabolic needs requires further investigation before it can be excluded as a contributory mechanism. Regardless of the mechanism, urine concentration in burned patients can be inappropriate, as judged by the plasma tonicity, but does fall with further dilution of plasma. This suggests a resetting of the osmostat for control of plasma tonicity, with a lower plasma tonicity threshold at which AVP is released. Studies over a wider range of plasma tonicity in a larger number of patients will be needed to determine if there is an additional altered sensitivity of AVP release to increments in plasma tonicity above threshold. The observed altered control of plasma tonicity is not surprising in view of other previously observed burn injury-related derangements of hypothalamic function. These include increased sympathetic activity, elevated heat production and core-skin heat conductance, self-selection of a warmer ambient temperature of maximal comfort despite a higher core and mean skin temperature in burned patients than in control subjects, blunted growth hormone response to provocative stimuli (31), and failure

of plasma thyrotrophin to rise despite low concentrations of thyroid hormones (30).

Acknowledgments

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DISCUSSION

DR. DONALD S. GANN (Rhode Island Hospital, Providence 02902): I enjoyed this paper very much, and I also enjoyed the opportunity to read it in advance. I think Doctor Shirani and his colleagues have once again set a very high standard for us in terms of the execution of some very difficult clinical research studies in acutely ill patients. I think that is a standard we would all do well to try to emulate.

It seems to me very clear that the authors have demonstrated elevated vasopressin in the plasma in the face of marked dilution of the plasma. Nothing I am going to say subsequently should be taken to call into question in any way that primary finding, which is not only important substantiation of what many people have believed for some time, but represents the first such documentation.

I do have a couple of minor points, however, and one major one. First of all, in patients who have been severely injured, such as these patients, it isn't fair to use calculated osmolality, as Doctor Kenney will show this afternoon (Glucose and osmolality as predictors of injury severity, in press, *J. Trauma*, 1983), and as Doctor Boyd and Doctor Mansberger reported many years ago. After acute injury, plasma osmolality is elevated and remains elevated for many days, and the elevation in osmolality is not accounted for by such things as the normal electrolytes and glucose. Many of the constituents have not been satisfactorily identified in man, but there may be a significant elevation that the authors neglected. Nonetheless, it is obvious that if the urine osmolality is 500, that is going to be significantly larger than any elevation in plasma.

Second, the inability to excrete a water load may be depend-

ent on an additional circumstance beyond that summarized by the authors, namely, an *increase in proximal tubular reabsorption* of sodium chloride and water. Hastings Wright and I first described this some 20 years ago in surgical patients in the *Annals of Surgery* (**158:** 70, 1963). That inability is independent of vasopressin. Interestingly, enhanced proximal reabsorption of sodium is in part catecholamine dependent, and, as Doctor Shirani pointed out, catechols are uniformly elevated at this point in such patients. Thus, this mechanism may play a role in water retention after injury.

Finally, there is the question of whether this really is inappropriate secretion of vasopressin. In pioneering studies related to this, Leaf and Manby first showed that normal subjects who had voluntarily given blood had an inability to excrete a water load, and when they drank water developed dilutional hyponatremia that was sustained for some days despite the fact that these subjects were on ad lib food and water intake. Incidentally, such subjects will drink themselves voluntarily into hyponatremia.

They assumed there must be some volume signal that they were unable to define, that set in motion this persistent antidiuresis. Subsequently, Leaf, Bartter, Santos, and Wrong showed that after a similar volume loss there was not only sustained antidiuresis but there was sodium loss as the subjects drank water or were given a water load, despite the fact that the antidiuresis was not turned off. So, this suggests again that there is an occult volume signal that has not been defined, that is present in man and that may be behind the elevation of vasopressin in the present studies.

When Schwartz and Bartter described SIADH they defined it as the presence in patients with normal filtration rate and normal cortisol, of decreased plasma osmolality and of increased urine-to-plasma osmotic ratio, which was *less than* maximum, in the absence of any signal to stimulate vasopressin secretion.

That is the basic point I want to make—that volume, hypotonicity, pain, fear, and anxiety are all potent stimuli to vasopressin secretion. In the present study the authors have clearly excluded hypertonicity as a signal, and have controlled extremely well, I believe, to exclude pain as the likely explanation. However, there remains the possibility of the occult volume stimulus that I mentioned, as well as the emotional factors which are almost certainly present in these subjects.

So, the question really then devolves upon: Should the term SIADH be reserved for patients who meet the Schwartz-Bartter criteria in the absence of any known signal to stimulate vasopressin secretion? I believe the answer to that ought to be Yes.

I enjoyed the paper very much, and appreciate the opportunity to discuss it.

DR. GEORGE L. BLACKBURN (New England Deaconess Hospital, Boston, MA 02215): I wonder if the authors came across the work of Synn and Tamby, published in *SG&O* about 1973, showing an operative injury similar, if you will, inappropriate only in the fact that once initiated it seemed to last 5 days regardless of the type of resuscitation, and perhaps teleologically is there in case you do not have effective resuscitation and you need a very potent, effective means of negative free water clearance in order not to go into hemorrhagic shock or hypovolemia.

Then it would not be inappropriate but would mean that our resuscitation therapy should fit this fixed response that appears to last 3 to 5 days, and this degree of injury, to wit, the hypertonic saline resuscitation at the level of about 3 cc/kg/% total body burn, and that would again ask you to reconsider it as inappropriate and as one that was there before we got into measurements or into our current resuscitation regimens.

DR. LAWRENCE H. PITTS (Neurosurgery Service, San Francisco General Hospital, San Francisco, CA 94110): There is some additional information in the neurosurgical field having to do with these effects, to supplement Doctor Gann's comments. In the past, it was a standard part of the therapy for subarachnoid hemorrhage to dehydrate the patients somewhat. Recently, it has been found that patients who had this therapy have elevated levels of antidiuretic hormone, or ADH.

Other recent studies have suggested that there may be some other stimulus, some natriuretic factor, that causes the hypovolemia, and that the ADH secretion is actually an appropriate response. To examine that hypothesis, sequential measurements of vasopressin were made. It was found that ADH was not present initially after subarachnoid hemorrhage, but that the ADH level began to become elevated some days after the hemorrhage occurred, consistent with a relative hypovolemia and an appropriate antidiuretic response.

I would ask the author of this paper whether or not any sequential measurements of vasopressin were made in burn patients in this study.

DR. KHAN Z. SHIRANI (Closing): I enjoyed the comments from the floor and discussion of our paper by Doctor Gann. With regard to osmolality, all the values presented for the water loading tests were determined by freezing point depression and indicated hypotonic plasma, as did the calculated values, and the plasma sodium is probably the only important endogenous constituent that controls vasopressin secretion. We realize that there is an ongoing controversy over the definition of SIADH. Bartter and his colleagues consider hypertonic urine *vis à vis* plasma osmolality sufficient to determine SIADH. However, there are some authorities who require exclusion of hypovolemia and other stimuli known to release vasopressin before considering a diagnosis of SIADH.

Several years ago, Doctors Pruitt and Mason and colleagues showed that following a successful resuscitation, the plasma volume returns to normal after the second postburn day. The normalization of total blood volume on various postburn days has also been adequately documented by Doctors Rogers and Kurzman. With that information at hand, we studied our patients days to weeks following thermal trauma when they were in a stable condition, and as best we could clinically determine, they were not hypovolemic. Many patients with inappropriately elevated vasopressin levels had appreciable urinary losses of sodium, and this natriuresis to which Doctor Gann has alluded would be interpreted by some authorities as an evidence against volume deficit. Non-AVP mediated water retention due to increased proximal or distal tubular reabsorption of sodium chloride and water may explain the inability to excrete a water load in other patients, but it does not explain the hypotonicity seen in our patients nor their sodium excretion.

These are data from Robertson. [Slide] In order to elevate plasma vasopressin to the levels observed in our patients, one would expect a 20 to 25% volume deficit, and hypovolemia of this magnitude does not remain clinically unnoticed. A possibly altered tissue demand for volume during the postburn flow phase of hypermetabolism is difficult to rule out, and this may fall into the category of occult volume deficit. Additionally, sodium excretion would not rule out an occult volume signal if there were some factor independently promoting sodium excretion. But, one would expect more than an occult signal to be necessary to shift the osmostat to the extent we have seen. Admittedly, emotional factors may contribute towards vasopressin stimulation.

Doctor Blackburn has correctly mentioned the well-known early transient water retention of post-surgical patients. For

this reason, we elected to study our patients days to weeks after thermal injury in an attempt to minimize those early effects of trauma. In response to Doctor Pitts' question, we have not sequentially measured the vasopressin levels in these patients but have purposefully focused on the period beyond resuscita-tion when volume has been restored. Of course, I am not surprised to hear that volume deficit in his neurosurgical pa-tients was a stimulus for the release of vasopressin.

I would like to thank the Association for giving us the opportunity to present this paper.